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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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19587 U.S. PTO 60/529824 121603

TITLE OF THE INVENTION (280 characters max)

PHOSPHODIESTERASE INHIBITORS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* ☐ CD(s), Number

☐ Drawing(s) *Number of Sheets* ☒ Other (specify) Postcard, Certificate of Express Mailing

☐ Application Data Sheet. See 37 CFR 1.76

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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Respectfully submitted,

SIGNATURE

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Date

REGISTRATION NO. (*if appropriate*) 42,648

Docket Number: RLL-419PRVUS

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PROVISIONAL APPLICATION COVER SHEET
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Docket Number	RLL-419PRVUS	Type a plus sign (+) inside this box →	+

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CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10) Applicant(s): PALLE et al.			Docket No. RLL-419PRVUS
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Invention:

PHOSPHODIESTERASE INHIBITORS

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RLL-419PRVUS

PHOSPHODIESTERASE INHIBITORS

Field of the Invention

The present invention relates to purine derivatives, which can be used as selective phosphodiesterase (PDE) type IV inhibitors. Compounds disclosed herein can be useful in the treatment of asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases especially in humans. Processes for the preparation of disclosed compounds, pharmaceutical composition containing the disclosed compounds and their use as selective phosphodiesterase (PDE) type IV inhibitors are provided.

Background of the Invention

It is known that cyclic adenosine-3', 5'-monophosphate (cAMP) exhibits an important role of acting as an intracellular secondary messenger (E.W. Sutherland, and T.W. Roll, *Pharmacol.Rev.*, (1960) 12, 265). Its intracellular hydrolysis to adenosine 5'-monophosphate (AMP) causes number of inflammatory diseases or conditions, for example, psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis. The most important role in the control of cAMP (as well as of cGMP) levels is played by cyclic nucleotide phosphodiesterase (PDE) which represents a biochemically and functionally, highly variable superfamily of the enzyme; eleven distinct families with more than 15 gene products are currently recognized. Although PDE 1, PDE 2, PDE 3, PDE 4, and PDE 7 all use cAMP as a substrate, only the PDE 4 and PDE VII types are highly selective for hydrolysis of cAMP. Inhibitors of PDE, particularly the PDE 4 inhibitors, such as rolipram or Ro-1724 are therefore known as cAMP-enhancers. Immune cells contain type IV and type III PDE, the PDE type IV being prevalent in human mononuclear cells. Thus the inhibition of phosphodiesterase type IV has been a target for modulation and, accordingly, therapeutic invention in a range of disease processes.

The initial observation that xanthine derivatives such as theophylline or caffeine inhibit the hydrolysis of cAMP led to the discovery of the required hydrolytic activity in the cyclic nucleotide phosphodiesterase (PDE) enzymes. More recently, distinct classes of PDE have been recognized (J.A. Bervo and D.H. Reifsnyder, TIPS (1990) 11, 150) and their selective inhibition has led to improved drug therapy (C.D. Nicholus, R.A. Challiss and M. Shahid, TIPS (1991) 12, 19). Thus, it was recognized that inhibition of PDE IV could lead to inhibition of inflammatory mediator release (M.W. Verghese et. al, *J. Mol. Cell. Cardiol.*, (1989) 12 (Suppl.II), S 61) and airway smooth muscle relaxation (T. J. Trophy in *Directions for new Anti-Asthma Drugs*, eds S.R. O' Donnell and (G.A.Perssan, (1988) 37, Birkheuserverlag).

WO 03/002566 discloses purine derivatives as A2B adenosine receptor antagonists. WO 01/44260 discloses particular purines and uses of these compounds for the treatment of bone related disorders and cancer. WO 01/49688 discloses purine derivatives, process for their prepration and use thereof. WO 01/02400 and EP 1,221,444 disclose fused imidazole compounds and treatments of diabetes mellitus. WO 99/11643 discloses heterocyclyl-substituted ring-fused pyridines and pyrimidine as corticotropin releasing hormone (CRH) antagonists, said to be useful for treating CNS and stress-related disorders. WO 03/11864 discloses the preparation of triazolylimidazopyrimidines and triazolylimidazopyridines as antagonists of adenosine A2 receptor for treatment of Parkinson's disease. WO 96/06845 describes the preparation of substituted 9-alkyladenines as adenosine A1 receptor inhibitors. WO 01/00587 describes the preparation of azolylbenzamides and analogues for treating osteoporosis.

European Patent No. 544445 describes the preparation of furyl-substituted purines, oxazolopyrimidines and pteridines as adenosine antagonists. Japanese Patent No. 2002155082 describes the process for preparing adenine derivatives. U.S. Patent No. 6,028,076 discloses purine derivatives, which are useful for the treatment of cancer or viral diseases. U.S. Patent No. 5,723,468 describes the preparation of imidazopyridines and analogs as muscarinic agonists. U.S. Patent No. 6,130,333 describes the preparation of benzodioxolylbenzimidazoles and related compounds as phosphodiesterase inhibitors. U.S. Patent No. 6,228,859 and 6,413,975 disclose purine derivatives described as having phosphodiesterase IV inhibitory

activity. *Biochem. and Biophys. Res. Comm.*, 288, 427-434 (2001) discloses 9-benyladenine derivatives with selective phosphodiesterase-4 inhibiting properties.

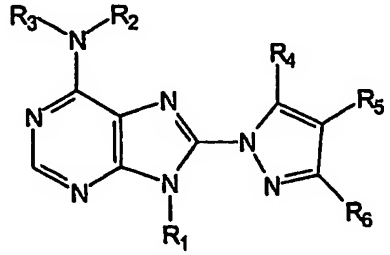
Summary of the Invention

Purine derivatives, which inhibit the PDE-IV enzyme and hence can be used for the treatment of asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases. Processes for the synthesis of these compounds are provided herein. Pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides of these compounds having the same type of activity are also provided.

Pharmaceutical compositions containing the compounds, which may also contain pharmaceutically acceptable carriers or diluents, which can be used for the treatment of asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases are also provided herein.

Other aspects will be set forth in accompanying description which follows and in part will be apparent from the description or may be learnt by the practice of the invention.

In accordance with one aspect, there are provided compounds having the structure of Formula I,



Formula I

their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides wherein

R_1 can represent hydrogen, alkyl, cycloalkyl, aryl, alkaryl, heteroaryl, heteroaryl alkyl, or heterocyclyl alkyl;

R_2 and R_3 independently represent hydrogen, alkyl, alkenyl, alkynyl, acyl, alkaryl, heteroaryl alkyl, or heterocyclyl alkyl;

R_2 and R_3 may together join to form three to eight membered cyclic rings, which may be optionally benzofused containing 0-3 heteroatom(s) selected from O, S and N, wherein the ring may be optionally substituted with one or more substituents selected from alkyl, alkenyl, alkynyl, cycloalkyl, carboxy, alkoxy, aryloxy, halogen, aryl, amino, substituted amino, alkaryl, heteroaryl, heterocyclyl, heteroarylalkyl and heterocyclyl alkyl; and

R_4, R_5 and R_6 are independently selected from hydrogen alkyl, aryl, heteroaryl, heterocyclyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, alkoxy, thioalkoxy, amino, and substituted amino;

with the provisos that when R_2 is hydrogen, R_3 cannot be hydrogen, alkaryl or heteroaryl alkyl; when R_2 is alkyl, R_3 cannot be alkaryl or heteroaryl alkyl; when R_2 is alkaryl, R_3 cannot be hydrogen or alkyl; when R_2 is heteroaryl alkyl, R_3 cannot be alkyl; when R_1 is alkyl, R_2 and R_3 cannot be hydrogen and alkyl, respectively; and when R_1 is hydrogen; R_2 and R_3 cannot be hydrogen and alkyl, respectively.

The following definitions apply to terms as used herein:

The term "alkyl" unless otherwise specified, refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 20 carbon atoms. This term can be exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-hexyl, n-decyl, tetradecyl, and the like. An alkyl group may be substituted with one or more substituents(s) selected from alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted aminoaminocarbonyl, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, carboxy, carboxyalkyl, aryloxy, aminosulfonyl,

aminocarbonylamino, hydroxyamino, alkoxyamino, nitro, and $-S(O)_n R_7$ where R_7 is hydrogen, alkyl, aryl or heteroaryl and n is 0, 1 or 2. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxy-alkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, and $-S(O)_nR_7$, where R_7 and n are the same as defined earlier; or an alkyl group as defined above can be interrupted by 1-5 atom(s) or groups independently chosen from oxygen, sulfur, keto, thiocarbonyl and $-NR_8-$, where R_8 can be chosen from hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, or aryl. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, and $-S(O)_nR_7$, where n and R_7 are the same as defined earlier; or an alkyl group as defined above that can have substituents as defined above and can also be interrupted by 1-5 atoms or groups as defined above.

The term "alkenyl" unless otherwise specified, refers to a monoradical branched or unbranched unsaturated hydrocarbon, having, for example, from 2 to 20 carbon atoms with cis or trans geometry. Particular alkenyl groups include ethenyl or vinyl ($CH=CH_2$), 1-propylene or allyl ($-CH_2CH=CH_2$), iso-propylene ($-C(CH_3)=CH_2$), bicyclo[2.2.1]heptene, and the like. In the event that an alkenyl group is attached to a heteroatom, the double bond cannot be alpha to the heteroatom. An alkenyl group may be substituted with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, carboxy, carboxyalkyl, aryloxy, heterocyclyl, heteroaryl, aminosulfonyl, aminocarbonylamino, hydroxyamino, alkoxyamino, nitro and $-S(O)_nR_7$ wherein R_7 and n are the same as defined earlier; or one or more carbon atom(s) can be replaced by keto or thiocarbonyl. Unless otherwise constrained by the definition, all substituents may optionally be substituted by 1-3 substituent(s) chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, and $-S(O)_nR_7$, where R_7 and n are the same as defined earlier.

The term "alkynyl" unless otherwise specified, refers to a monoradical of an unsaturated hydrocarbon, having from 2 to 20 carbon atoms. Particular alkynyl groups

include ethynyl, (-C=CH), propargyl (or propynyl, -CH_2C=CH), and the like. In the event that an alkynyl group is attached to a heteroatom, the triple bond cannot be alpha to the heteroatom. An alkynyl group may be substituted with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, carboxy, carboxyalkyl, aryloxy, aminosulfonyl, aminocarbonylamino, hydroxyamino, alkoxyamino, nitro, heterocyclyl, heteroaryl, and $-S(O)_nR_7$, where R_7 and n are the same as defined earlier; or one or more carbon atom can be replaced by keto or thiocarbonyl. Unless otherwise constrained by the definition, all substituents may optionally be substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, and $-S(O)_nR_7$, where R_7 and n are the same as defined earlier.

The term "cycloalkyl" refers to (un)saturated cyclic hydrocarbon of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, cyclopropylene, cyclobutylene and the like, or multiple ring structures such as adamantanyl and bicyclo [2.2.1]heptane, or cyclic alkyl groups to which is fused an aryl group, for example, indane, and the like.

"Substituted amino" unless otherwise specified, refers to a group $-N(R_8)_2$ wherein each R_8 is independently selected from hydrogen (provided that both R_8 are not hydrogen), alkyl, alkenyl, alkynyl, alkaryl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, SO_2R_7 wherein R_7 is the same as defined above, C(=O)R_7 wherein R_7 is the same as defined above, and C(=O)OR_9 wherein R_9 is selected from alkyl, alkaryl, heteroarylalkyl, aryl, heteroaryl and heterocyclyl. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, and $-S(O)_nR_7$, where R_7 and n are the same as defined earlier.

The term "alkoxy" denotes the group O-alkyl wherein alkyl is the same as defined above.

The term "alkaryl" refers to $(CH_2)_p$ aryl, wherein p is an integer in the range of 1-6 and aryl is as defined below.

The term "aryl" herein refers to phenyl, biphenyl or naphthyl systems and the like, optionally substituted with 1 to 3 substituents selected from halogen, hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, aryloxy, cyano, nitro, carboxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, $-C(=O)R_{10}$ wherein R_{10} is selected from hydrogen, alkyl, cycloalkyl, aryl, alkaryl, amino, substituted amino, hydroxy, alkoxy, heteroaryl, heterocyclyl, and $(CH_2)_{0-3}C(=O)N(R_8)_2$, wherein R_8 is same as defined earlier.

The term "carboxy" as defined herein refers to $-C(=O)O-R_{11}$ wherein R_{11} is selected from hydrogen, alkyl, alkenyl, alkynyl or cycloalkyl.

The term "heteroaryl" unless otherwise specified refers to an aromatic ring structure containing 2 to 6 carbon atoms, or a bicyclic aromatic group having 4 to 10 carbon atoms, with one or more heteroatom(s) independently selected from N, O and S, optionally substituted with 1 to 3 substituent(s) selected from halogen, hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, carbamoyl, aryl, alkoxy, alkaryl, cyano, oxo, nitro, optionally substituted amino (wherein the substituents are selected from alkyl, alkenyl, alkynyl, cycloalkyl, or aryl); carboxy, $-C(=O)R_{11}$ wherein R_{11} is the same as defined earlier and $-C(=O)N(R_8)_2$ wherein R_8 is the same as defined earlier. Examples of heteroaryl groups are pyridinyl, pyridazinyl, pyrimidinyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, triazinyl, furanyl, benzofuranyl, indolyl, benzothiazolyl, benzoxazolyl, and the like.

The term 'heterocyclyl" unless otherwise specified refers to a non aromatic cycloalkyl group having 5 to 10 atoms in which 1 to 3 carbon atoms in a ring are replaced by heteroatoms selected from O, S and N, and are optionally benzofused or fused heteroaryl of 5-6 ring members and/or are optionally substituted wherein the substituents are selected from halogen, hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, carbamoyl, aryl, alkoxy, alkaryl, cyano, nitro, oxo, optionally substituted amino wherein the substituents are selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl; carboxy, $C(=O)R_{10}$ wherein R_{10} is the same as defined earlier; $C(=O)N(R_8)_2$ wherein R_8 is the same as defined earlier. Examples of

heterocyclyl groups are tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, piperidinyl, piperazinyl, dihydrobenzofuryl, dihydroindolyl, and the like.

"Heteroarylalkyl" refers to alkyl-heteroaryl group wherein the alkyl and heteroaryl are the same as defined earlier. "Heterocyclylalkyl" refers to alkyl-heterocyclyl group wherein the alkyl and heterocyclyl are the same as defined earlier. The term "acyl" as defined herein refers to $-C(=O)R_{10}$, wherein R_{10} can be the same as defined earlier.

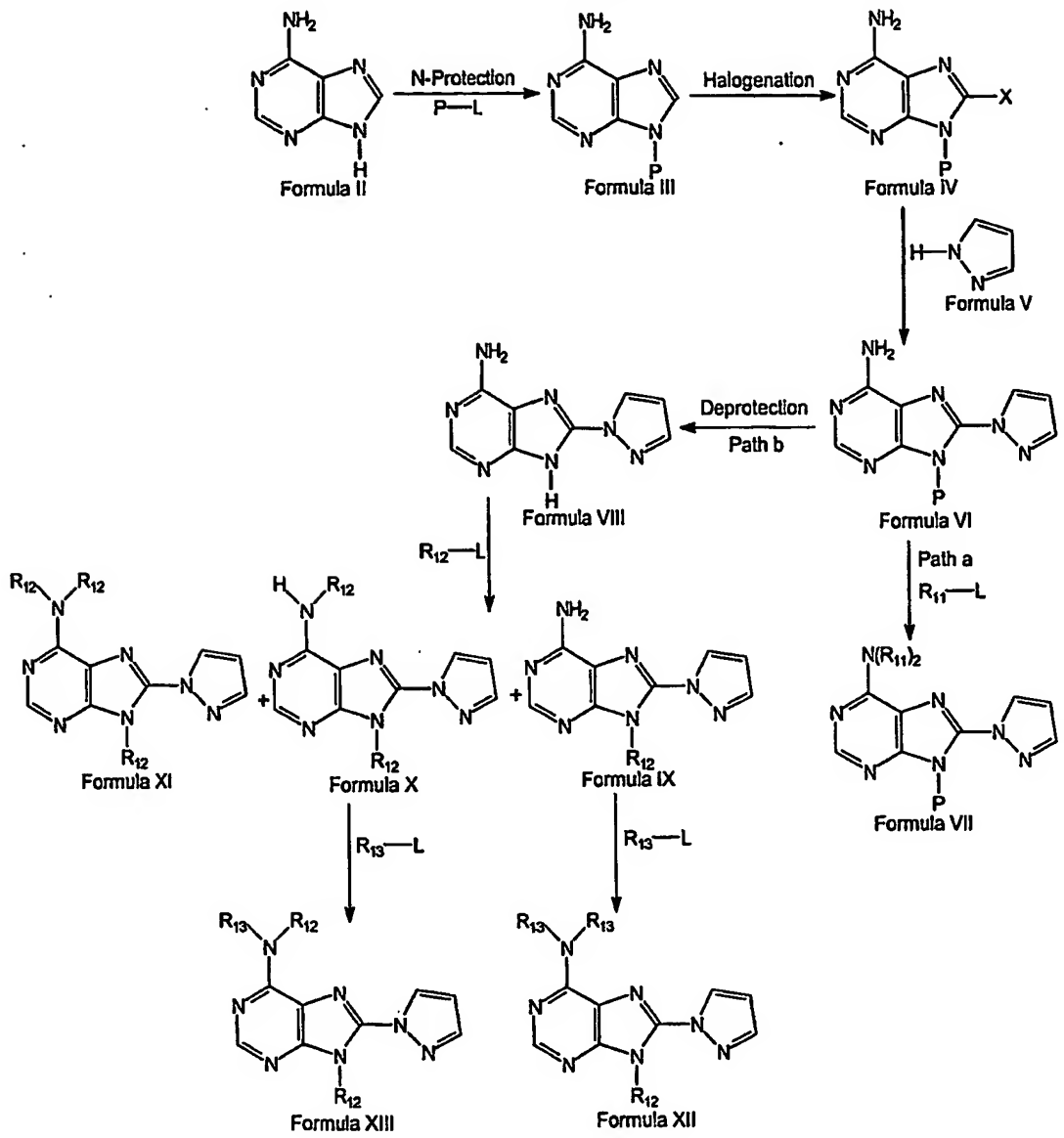
The term "halogen" as defined herein refers to F, Cl, Br or I.

In accordance with yet another aspect, there are provided processes for the preparation of the compounds as described herein.

Detailed Description of the Invention

The compounds disclosed herein may be prepared by techniques well known in the art. In addition, these compounds may be prepared following illustrative reaction sequences as depicted in Schemes I, II and III.

Scheme I



Compounds of Formula VII can be prepared according to Scheme I (Path a). Thus, N-protecting a compound of Formula II with a compound of Formula P-L (wherein P is protecting group, such as alkaryl, and L is leaving atom or group, such as Cl, Br, F, I) gives a compound of Formula III, which on halogenation gives a compound of Formula IV (wherein X is halogen), which on reaction with pyrazole of Formula V gives a compound of Formula

VI, which is finally reacted with a compound of Formula R_{11}-L to give a compound of Formula VII (wherein R_{11} represents R_3 , and R_3 is the same as defined earlier).

The N-protection of a compound of Formula II to give a compound of Formula III can be carried out, for example, by following procedures described in *J. Heterocyclic Chem.* Vol. 19, 249-251 (1982), *J. Heterocyclic Chem.* Vol 1, 115-120 (1964), or *Bioorg. Med. Chem.* Vol 6, 523-533 (1998).

The halogenation of a compound of Formula III can be carried out in the presence of a halogenating agent such as N-bromosuccinamide, N-chlorosuccinimide or N-iodosuccinimide. The halogenation of a compound of Formula III can be carried out in a solvent such as dimethylformamide, dimethylsulphoxide or tetrahydrofuran. The reaction of a compound of Formula IV with a compound of Formula V to give a compound of Formula VI can be carried out in a solvent such as dimethylformamide, dimethylsulphoxide or tetrahydrofuran. The reaction of a compound of Formula IV with a compound of Formula V can be carried out in the presence of a base such as sodium hydride, lithium hydride, and lithium diisopropyl amide or sodium cyanoborohydride. The reaction of a compound of Formula VI (path a) with a compound of Formula R_{11}-L to a compound of Formula VII can be carried out in a solvent such as toluene, tetrahydrofuran, dimethylformamide or dimethylsulphoxide. The reaction of a compound of Formula VI with a compound of Formula R_{11}-L can be carried out in the presence of a base such as pyridine, triethylamine, potassium carbonate, lithium hydride or sodium hydride.

The compound(s) prepared following Scheme I path a are:

–N-Acetyl-N-(9-benzyl-8-pyrazol-1-yl-9H-purin-6-yl) acetamide (Compound No. 2)

–N-benzoyl-N-(9-benzyl-8-pyrazol-1-yl-9H-purin-6-yl) benzamide (Compound No. 3)

–N-(9-Benzyl-8-pyrazol-1-yl-9H-purin-6-yl)-2,2-dimethylpropionamide (Compound No. 1)

The compounds of Formulae XI-XIII can be prepared according to Scheme I (Path b). Thus, deprotecting a compound of Formula VI gives a compound of Formula VIII, which on

reaction with a compound of Formula R_{12}-L (wherein R_{12} is alkaryl and L is leaving atom or group) gives a compound of either:

– Formula IX, which is finally reacted with a compound of Formula R_{13}-L (wherein R_{13} represents R_2 or R_3 except hydrogen and R_2 and R_3 are the same as defined earlier) to give a compound of Formula XII,

– Formula X, which is finally reacted with a compound of Formula R_{13}-L to give a compound of Formula XIII (wherein R_{13} is the same as defined above), or

– Formula XI (wherein R_{12} is the same as defined above).

The deprotection of a compound of Formula VI (Path b) to give a compound of Formula VIII can be carried out following the procedure described in *Protective Groups in Organic Synthesis,* Greene et al., Third Edition, 1999, Wiley Interscience Publications, pp-579-580.

The reaction of a compound of Formula VIII with a compound of Formula R_{13}-L to give compound of Formula IX, X and XI can be carried out, for example, by following procedures described in *J. Heterocyclic Chem.* Vol. 19, 249-251 (1982), *J. Heterocyclic Chem.* Vol. 1, 115-120(1964) or *Bioorg. Med. Chem.* Vol. 6, 523-533 (1998).

The reaction of compound of Formula IX with a compound of Formula R_{13}-L to give a compound of Formula XII can be carried out in a solvent such as toluene, tetrahydrofuran, dimethylformamide or dimethylsulphoxide. The reaction of a compound of Formula IX with a compound of Formula R_{13}-L can be carried out in the presence of a base such as pyridine, triethylamine, potassium carbonate, lithium hydride or sodium hydride.

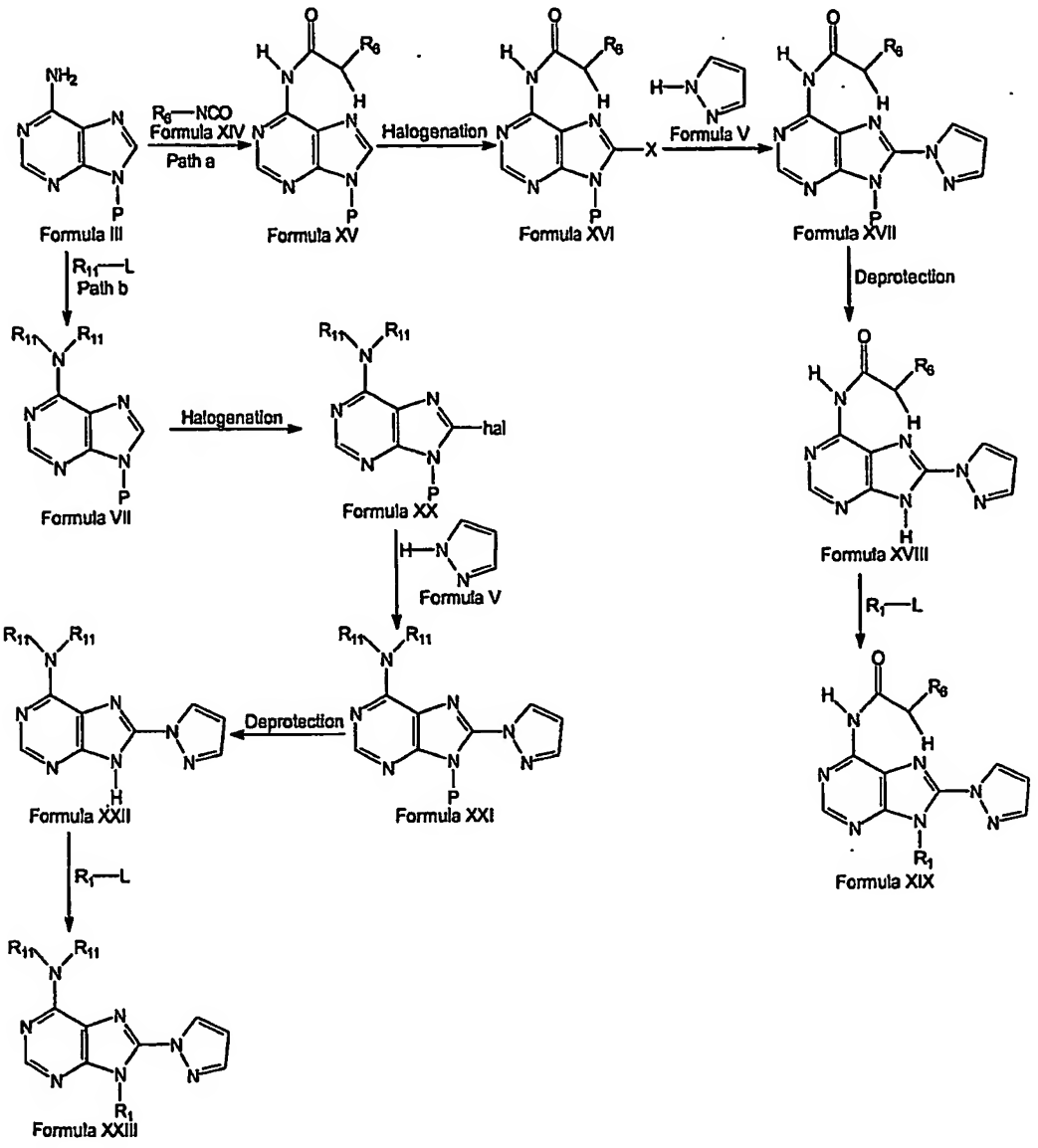
The reaction of a compound of Formula X with a compound of Formula R_{13}-L to give a compound of Formula XIII can be carried out in a solvent such as toluene, tetrahydrofuran, dimethylformamide or dimethylsulphoxide. The reaction of a compound of Formula X with a compound of Formula R_{13}-L can be carried out in the presence of a base such as pyridine, triethylamine, potassium carbonate, lithium hydride or sodium hydride.

The compounds prepared following Scheme I, path b are:

-Bis-(2-chlorobenzyl)-[9-(2-chlorobenzyl)-8-pyrazole-1-yl-9H-purin-6-yl]-amine (Compound No. 4)

-1-(9-Benzyl-8-pyrazol-1-yl-9H-purin-6-yl)-3-(4-chlorophenyl) urea (Compound No. 6)

Scheme II



The compounds of Formula XIX can be prepared according to Scheme II (Path a). Thus, reacting a compound of Formula III with a compound of Formula XIV gives a compound of Formula XV (wherein P is a protecting group and R_6 is the as defined earlier), which on halogenation gives a compound of Formula XVI (wherein X is halogen), which on

treatment with pyrazole of Formula V gives a compound of Formula XVII, which on deprotection gives a compound of Formula XVIII, which is finally treated with a compound of Formula R_1-L gives a compound of Formula XIX (wherein R_1 is the same as defined earlier).

The reaction of a compound of Formula III with a compound of Formula XIV can be carried out in a solvent such as dichloromethane, dichloroethane or dimethylformamide. The halogenation of a compound of Formula XV to give a compound of Formula XVI can be carried out in a solvent such as dimethylformamide, dimethylsulphoxide or tetrahydrofuran. The halogenation of a compound of Formula XV to give a compound of Formula XVI can be carried out in the presence of a halogenating agent such as N-bromosuccinimide, N-chlorosuccinimide or N-iodosuccinimide.

The reaction of a compound of Formula XVI with a compound of Formula V can be carried out in a solvent such as dimethylformamide, dimethylsulphoxide or tetrahydrofuran. The reaction of a compound of Formula XVI with a compound of Formula V can be carried out in the presence of a suitable base such as sodium hydride, lithium hydride or sodium cyanoborohydride.

The deprotection of a compound of Formula XVII to give a compound of Formula XVIII can be carried out by following the procedure described in *Protective Groups in Organic Synthesis*, Greene et al., Third Edition, 1999, Wiley Interscience Publications, pp-579-580.

The reaction of a compound of Formula XVIII with a compound of Formula R_1-L to give a compound of Formula XIX can be carried out, for example, by following procedures described in *J. Heterocyclic Chem.* Vol. 19, 249-251 (1982), *J. Heterocyclic Chem.* Vol. 1, 115-120 (1964) or *Bioorg. Med. Chem.* Vol. 6, 523-533 (1998).

The compounds of Formula XXIII can be prepared according to Scheme II (Path b). Thus reacting a compound of Formula III with a compound of Formula R_{11}-L (wherein R_{11} represents R_3 and R_3 is the same as defined earlier and L is the same as defined above) gives a compound of Formula VII (wherein P is a protecting group as defined earlier and R_{11} is as

defined earlier), which on halogenation gives a compound of Formula XX (wherein hal is halogen), which on treatment with pyrazole of Formula V gives a compound of Formula XXI, which on deprotection gives a compound of Formula XXII, which is finally treated with a compound of Formula R_1-L to give a compound of Formula XXIII (wherein R_1 is the same as defined earlier).

The reaction of a compound of Formula III with a compound of formula R_{11}-L to give a compound of Formula VII can be carried out in the presence of a base such as pyridine, triethylamine, potassium carbonate, lithium hydride or sodium hydride.

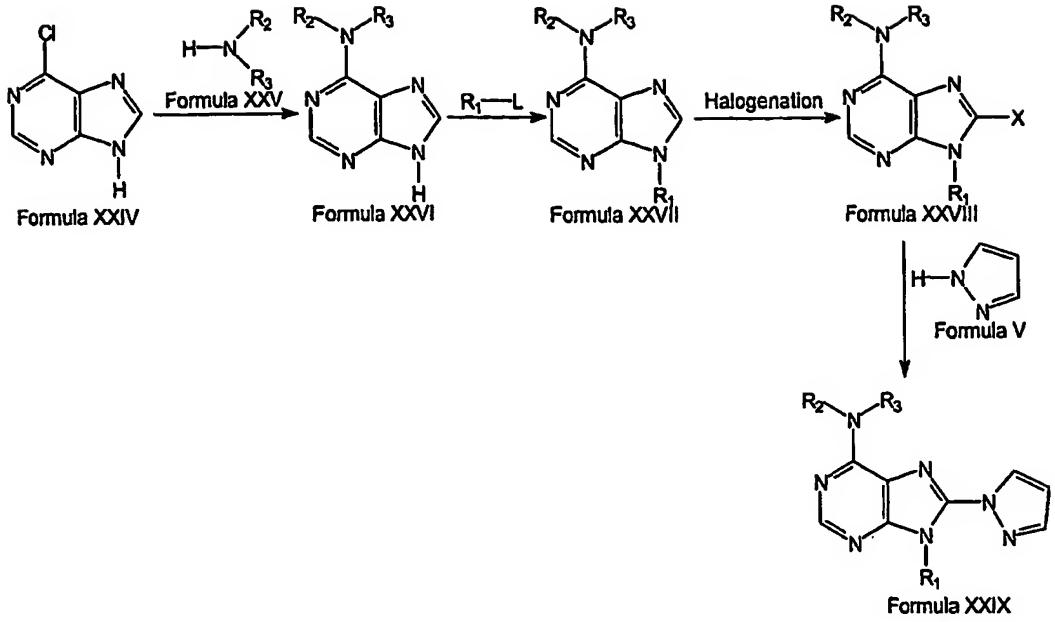
The halogenation of a compound of Formula VII to give a compound of Formula XX can be carried out in a solvent such as dimethylformamide, dimethylsulphoxide or tetrahydrofuran. The halogenation of a compound of Formula VII to give a compound of Formula XX can be carried out in the presence of a halogenating agent such as N-bromosuccinimide, N-chlorosuccinimide or N-iodosuccinimide.

The reaction of a compound of Formula XX with pyrazole of Formula V to give a compound of Formula XXI can be carried out in a solvent such as dimethylformamide, dimethylsulphoxide or tetrahydrofuran. The reaction of a compound of Formula XX with pyrazole of Formula V can be carried out in a base such as sodium hydride, lithium hydride or sodium cyanoborohydride.

The deprotection of a compound of Formula XXI to give a compound of Formula XXII can be carried out by following the procedure described in *Protective Groups in Organic Synthesis,* Greene et al., Third Edition, 1999, Wiley Interscience Publications, pp-579-580.

The reaction of a compound of Formula XXII with a compound of Formula R_1-L to give a compound of Formula XXIII can be carried out following the procedure described in *J. Heterocyclic Chem.* Vol. 19, 249-251 (1982), *J. Heterocyclic Chem.* Vol. 1, 115-120 (1964) or *Bioorg. Med. Chem.* Vol. 6, 523-533 (1998).

Scheme III



The compounds of Formula XXIX can be prepared according to Scheme III. Thus, reacting a compound of Formula XXIV with a compound of Formula XXV gives a compound of Formula XXVI (wherein R_2 and R_3 are the same as defined earlier), which on treatment with a compound of Formula R_1-L gives a compound of Formula XXVII (wherein R_1 is the same as defined earlier), which on halogenation gives a compound of Formula XXVIII (wherein X is halogen), which is finally reacted with pyrazole of Formula V to give a compound of Formula XXIX (Formula I wherein R_4, R_5 and R_6 are hydrogen).

The reaction of a compound of Formula XXVI with a compound of Formula R_1-L can be carried out following the procedure as described in *J. Heterocyclic Chem.* Vol. 19, 249-251 (1982), *J. Heterocyclic Chem.* Vol. 1, 115-120 (1964) or *Bioorg. Med. Chem.* Vol. 6, 523-533 (1998).

The halogenation of a compound of Formula XXVII to give a compound of Formula XXVIII can be carried out in a solvent such as dimethylformamide, dimethyl sulphoxide or tetrahydrofuran. The halogenation of compound of Formula XXVII to give a compound of Formula XXVIII can be carried out in the presence of a halogenating agent such as N-bromosuccinimide, N-chlorosuccinimide or N-iodosuccinimide.

The reaction of a compound of Formula XXVIII with pyrazole of Formula V to give a compound of Formula XXIX can be carried out in a solvent such as dimethylformamide, dimethylsulphoxide or tetrahydrofuran. The reaction of a compound of Formula XXVIII with pyrazole of Formula V can be carried out in the presence of a such as sodium hydride, lithium hydride or sodium cyanoborohydride.

Compounds prepared following Scheme III are:

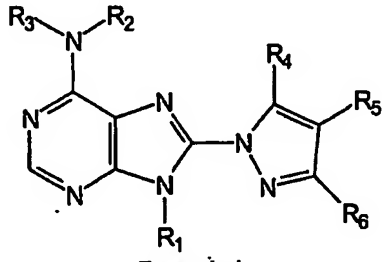
-(9-Benzyl-8-pyrazol-1-yl-9H-purin-6-yl) methylamine (Compound No. 5)

–5-(6-Methylamino-8-pyrazol-1-yl-purin-9-yl-methyl)-oxazolidin-3-one (Compound No. 7)

–9-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-diydro-isoxazol-5-ylmethyl]-8-pyrazol-1-yl-9H-purin-6-yl}-methyl-amine (Compound No. 8)

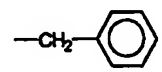
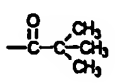
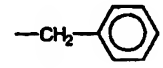
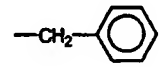
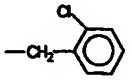
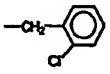
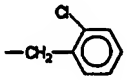
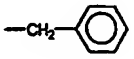
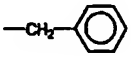
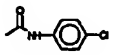
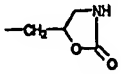
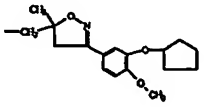
An illustrative list of particular compounds disclosed herein is given below in Table I.

Table I



Formula I

(wherein R_4=R_5=R_6=H)

Compound No.	R_1	R_2	R_3
1.		H	
2.			
3.			
4.			
5.		H	CH_3
6.		H	
7.		H	CH_3
8.		H	CH_3

In the above schemes, where specific bases, condensing agents, reducing agents hydrolyzing agents, solvents, etc. are used, it is to be understood that other specific bases, condensing agents, reducing agents, hydrolyzing agents, solvents known to those skilled in the art may also be used. Similarly, the reaction temperature and duration of the reaction may be adjusted as desired.

Examples

Example 1: Synthesis of methyl (9H-purin-6-yl)-amine

A solution of 6-chloropurine (0.1 gm, 0.6472 mmole) in methylamine (1.5 ml) was stirred at 100°C in an oil bath for 20 hours. The resulting reaction mixture was evaporated off

and the yellow semi-solid residue was obtained, which on treatment with ethyl alcohol gave the title organic compound.

Yield: 90 mg

Example 2: Synthesis of 9-benzyl-9H-purin-6-ylamine

To a suspension of adenine (3 gm, 22.22 mmole) in benzene (55.5 ml) was added sodium hydroxide solution (9.8 ml of 10%) followed by the addition of tetra n-butyl ammonium bromide (1.430 gm, 4.44 mmole). To the resulting reaction mixture, benzyl chloride (4.21 g, 3.8 ml, 33.3 mmole) was added under constant stirring. The reaction mixture was heated in an oil bath maintained at 80-83°C for 12 hours. The reaction mixture was cooled at room temperature to yield the crude organic compound, which was purified by column chromatography using methanol: ethyl acetate solvent mixture as an eluent.

Yield = 1.5 gm.

Example 3: Synthesis of 9-benzyl-8-bromo-9H-purin-6-yl amine

To the solution of 9-benzyl-9H-purin-6-ylamine (0.15 gm, 0.66 mmole, Example 2) in dry dimethylformamide (0.7 ml) was added N-bromosuccinimide (0.2373 g, 1.33 mmole). Reaction mixture was stirred for 2 hours at room temperature. Dimethylformamide was evaporated off under reduced pressure. To the residue thus obtained was added methanol (5-6 ml) to yield the title organic compound.

Yield = 0.14 gm

Example 4: Synthesis of 9-benzyl-8-pyrazol-1-yl-9H-purin-6-ylamine

To the solution of pyrazole (0.3446 gm, 5.065 mmole) and sodium hydride (0.13 gm, 5.526 mmole) in dry dimethylformamide (0.7 ml) was added 9-benzyl-8-bromo-9H-purin-6-yl amine (0.14 gm, 0.4605 mmole, Example 2). The reaction mixture was stirred at 100°C for 22 hours. Dimethylformamide was evaporated off under reduced pressure. To the residue thus obtained, water (10 ml) was added. The organic compound was extracted with toluene (2×10 ml) and dried over sodium sulphate and subsequently concentrated under reduced pressure to

yield the crude organic compound. The crude organic compound thus obtained was treated with methanol to yield the title organic compound.

Yield = 0.1 gm

Example 5: Synthesis of 8-pyrazol-1-yl-9H-purin-6-ylamine

The 9-benzyl-8-pyrazol-1-yl-9H-purin-6-ylamine (1.5 gm, 5.1546 mmol, Example 4) was taken in dry methanol in formic acid solution (90%, 3.04 ml). To it ammonium formate (6.0938 gm) was added, followed by addition of palladium on carbon (4.57 gm, 10%) under nitrogen atmosphere. The reaction mixture was stirred for 30 minutes at room temperature, followed by refluxing at 50-55°C for 24 hours. Palladium on carbon was filtered and the black solid thus obtained was washed with 200 ml of hot methanol. Methanol was evaporated off under reduced pressure to afford an organic compound, which was finally treated with brine, filtered, concentrated and dried to yield the title organic compound.

Yield = 0.64 gm

Example 6: Synthesis of Bis-(2-chlorobenzyl)-[9-(2-chlorobenzyl)-8-pyrazol-1-yl-9H-purin-6-yl]-amine (Compound No. 4)

To a solution of 8-pyrazol-1-yl-9H-purin-6-ylamine (0.05 gm, 0.248 mmole, Example 5) in dry dimethylformamide (0.5 ml) was added potassium carbonate (0.1373 gm, 0.995 mmole). To the resulting reaction mixture was added 2-chlorobenzylbromide (0.0102gm, 0.4975 mmole) and the reaction was allowed to stirr for 16 hour at 110°C. The reaction mixture was diluted with methanol. The inorganic salts thus separated were filtered and washed with methanol. The filtrate was concentrated to dryness to yield the crude organic compound. The crude organic compound was purified over column chromatography by using methanol: ethyl acetate solvent mixture as an eluent to yield title organic compound.

Yield = 27 mg.

m.pt: oil
^{1}HNMR ($CDCl_3$): δ 8.38 (s, 1H), 8.00 (s, 1H), 7.75 (s, 1H), 7.18-7.36 (m, 12H), 6.40 (s, 1H), 5.87 (s, 2H), 5.78 (s, 2H), 5.08 (s, 2H)
Mass (M^++1): m/z 574.5

Example 7: Synthesis of 1-(9-Benzyl-8-pyrazol-1-yl-9H-purin-6-yl)-3-(4-chlorophenyl) urea (Compound No. 6)

To a solution of 9-benzyl-8-pyrazol-1-yl-9H-purin-6-ylamine (0.07 gm, 0.2405 mmole, Example 4) in dichloroethane (0.3 ml) and dimethylformamide (0.3 ml) was added 4-chloropenyl isocyanate (0.0369 gm, 0.240 mmole). The resulting reaction mixture was stirred at room temperature for 2 hours. The solid compound thus obtained was filtered off and washed with dichloroethane. The product was purified by recrystallization from methanol.

Yield = 40 mg.
m.pt: 232-233 ^{0}C
^{1}HNMR ($CDCl_3$): δ 8.65 (s, 1H), 8.32 (s, 1H), 7.85 (s, 1H), 7.22-7.34 (m, 9H), 6.54 (s, 1H), 6.05 (s, 2H), 7.59-7.26 (d, 2H)
Mass (M^++1): m/z 445.14

Example 8: Synthesis of N-benzoyl-N-(9-benzyl-8-pyrazol-1-yl-9H-purin-6-yl)-benzamide (Compound No. 3)

To a solution of 9-benzyl-8-pyrazol-1-yl-9H-purin-6-ylamine (0.1027 gm, 0.35 mmole, Example 4) in pyridine (0.5 ml) was added benzoylchloride (1.2 ml, 1.05 mmole) and the solution was heated in an oil bath maintained at 80-85°C for 40 minutes. Toluene was added to the resulting reaction mixture followed by removal of pyridine under reduced pressure. To the residue thus obtained was added aqueous sodium bicarbonate solution and the organic compound was extracted with chloroform (2×15 ml). The organic layer was dried over sodium sulphate, concentrated and dried to give an oily residue, which was finally treated with ether to yield the title organic compound.

Yield = 80 mg.
m.pt: 197-198 ^{0}C
^{1}HNMR ($CDCl_3$): δ 8.70 (s, 1H), 8.30 (s, 1H), 8.13 (s, 1H), 7.24-7.86 (m, 15H), 6.45 (s, 1H), 6.05 (s, 2H)
Mass (M^++1): m/z 500.4

By following the same procedure and by its using the suitable intermediates the following compounds were obtained.

–N-(9-Benzyl-8-pyrazol-1-yl-9H-purin-6-yl)-2,2-dimethyl propionamide (Compound No. 1)

m.pt: 124-125 ^{0}C
^{1}HNMR ($CDCl_3$): δ 8.80 (s, 1H), 8.35 (s, 1H), 7.85 (s, 1H), 7.21-7.26 (m, 5H), 6.02 (s, 2H), 1.41 (s, 9H)
Mass (M^++1): m/z 376.3

–N-Acetyl-N-(9-benzyl-8-pyrazol-1-yl-9H-purin-6-yl)-acetamide (Compound No. 2)

m.pt: oil
^{1}HNMR ($CDCl_3$): δ 8.96 (s, 1H), 8.43 (s, 1H), 7.87 (s, 1H), 7.18-7.37 (m, 5H), 6.53 (s, 1H), 6.02 (s, 2H), 2.293 (s, 6H)
Mass (M^++1): m/z 376.5

Example 9: Synthesis of (9-Benzyl-8-pyrazol-1-yl-9H-purin-6-yl) methylamine (Compound No. 5)

Step a: Synthesis of methyl-(9-benzyl-9H-purin-6-yl)amine

The title compound was prepared following the procedure as described in Example 2 by using methyl-(9H-purin-6-ylamine) (Example 1) in place of adenine.

Step b: Synthesis of methyl-(9-benzyl-8-bromo-9H-purin-6-yl)amine

The title compound was prepared following the procedure as described Example 3 by using the compound obtained from step a above in place of compound prepared in Example 2.

Step c: Synthesis of 9-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4, 5-diydroisoxazol-5-ylmethyl]-8-pyrazol-1-yl-9H purin-6-ylamine

The title organic compound was prepared following the procedure as described in Example 4 by using the compound obtained from step b above in place of 9-benzyl-8-bromo-9H-purin-6-ylamine.

m.pt: 115 ^{0}C
^{1}HNMR ($CDCl_3$): δ 8.42-8.43 (d, 1H), 7.96-7.99 (d, 1H), 7.63 (s, 1H), 7.35-7.42 (m, 5H), 6.74 (s, 1H), 6.43-6.45 (t, 1H), 5.58 (s, 2H), 3.19 (s, 3H)
Mass (M^++1): m/z 306.20

By following the same procedure and by utilizing the suitable intermediates the following compound(s) are also obtained.

–5-(6-Methylamino-8-pyrazol-1-yl-purin-9-ylmethyl)-oxazolidin-3-one (Compound No. 7)

–9-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4, 5-diydro-isoxazol-5-ylmethyl]-8-pyrazol-1-yl-9H-purin-6-yl-methyl amine (Compound No. 8)

Example 10: Efficacy of compounds as PDE IV inhibitors

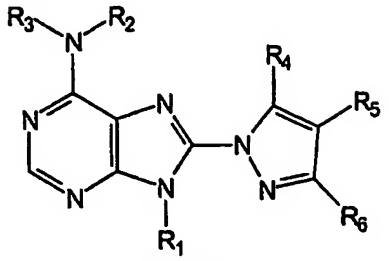
PDE-IV Enzyme Assay

The efficacy of compounds of PDE-4 inhibitors was determined by an enzyme assay using U937 cell cytosolic fraction (BBRC, 197: 1126-1131, 1993). Hydrolysis of cAMP to AMP was monitored using HPLC and [^{3}H]cAMP in the sample was detected using FLO-ONE Detector.

The enzyme preparation was incubated in the presence and absence of the test compound for 30 min and amount of [3H]cAMP was measured in the sample. IC_{50} valves for compounds tested are found to be in the range of from about 1 nmol to about 10 nmol.

We claim:

1. Compounds having the structure of Formula I,



Formula I

their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides wherein

R_1 represents hydrogen, alkyl, cycloalkyl, aryl, alkaryl, heteroaryl, heteroaryl alkyl, or heterocyclyl alkyl;

R_2 and R_3 independently represent hydrogen, alkyl, alkenyl, alkynyl, acyl, alkaryl, heteroaryl alkyl, or heterocyclyl alkyl;

R_2 and R_3 may together join to form three to eight membered cyclic rings, which may be optionally benzofused containing 0-3 heteroatom(s) selected from O, S and N, wherein the ring may be optionally substituted with one or more substituents selected from alkyl, alkenyl, alkynyl, cycloalkyl, carboxy, alkoxy, aryloxy, halogen, aryl, amino, substituted amino, alkaryl, heteroaryl, heterocyclyl, heteroarylalkyl and heterocyclyl alkyl; and

R_4, R_5 and R_6 are independently selected from hydrogen alkyl, aryl, heteroaryl, heterocyclyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, alkoxy, thioalkoxy, amino, and substituted amino;

with the provisos that when R_2 is hydrogen, R_3 cannot be hydrogen, alkaryl or heteroaryl alkyl; when R_2 is alkyl, R_3 cannot be alkaryl or heteroaryl alkyl; when R_2 is alkaryl, R_3 cannot be hydrogen or alkyl; when R_2 is heteroaryl alkyl, R_3 cannot be alkyl; when R_1 is alkyl, R_2

and R_3 cannot be hydrogen and alkyl, respectively; and when R_1 is hydrogen; R_2 and R_3 cannot be hydrogen and alkyl, respectively.

Abstract

The present invention relates to purine derivatives, which can be used as selective phosphodiesterase (PDE) type IV inhibitors. Compounds disclosed herein can be useful in the treatment of asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases especially in humans. Processes for the preparation of disclosed compounds, pharmaceutical composition containing the disclosed compounds and their use as selective phosphodiesterase (PDE) type IV inhibitors are provided.